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Mechanisms of Action Involved in the In Vivo Gastroprotective Response of Fruits: A Systematic Review

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ABSTRACT

Gastrointestinal diseases remain a significant global health concern, primarily due to the limitations of current pharmacological treatments, which often come with adverse side effects and high recurrence rates. This situation highlights the urgent need for safer and more effective alternatives. Natural products, particularly fruits, have gained considerable attention as potential gastroprotective agents due to their rich content of bioactive compounds that possess antioxidant, anti-inflammatory, and cytoprotective properties. This systematic review work includes 48 studies aimed at elucidating the mechanisms of action through which fruits exert gastroprotective effects. The analysis identified several key mechanisms, such as enhancing antioxidant defenses with reduction of oxidative stress, modulating prostaglandin synthesis with suppression of pro-inflammatory cytokines, increasing nitric oxide (NO) production, activating potassium (K^+) channels involved in protecting the gastric mucosa from injury, and regulating gastric acid secretion. Among the various fruit species cited, Hylocereus polyrhizus (dragon fruit), Phoenix dactylifera (date fruit), Vaccinium corymbosum (blueberry), Punica granatum (pomegranate), Passiflora edulis (passion fruit), Citrus sinensis (sweet orange), Aegle marmelos (bael), and Aronia melanocarpa (chokeberry) demonstrated relevant gastroprotective efficacy. The evidence suggests that incorporating these fruits into the diet may help prevent gastric damage and manage gastrointestinal disorders. However, while preclinical findings are promising, further well-designed clinical trials are necessary to validate their therapeutic potential.

1 | Introduction

Gastrointestinal diseases, such as peptic ulcers, represent a significant challenge for global public health, affecting millions of people annually (Jin et al. 2024). Conventional treatments include the use of antacids, proton pump inhibitors (PPIs), and H2 receptor antagonists, which, although effective, may be associated with side effects and symptom recurrence (Bereda

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2022). In this context, the search for natural therapeutic alternatives has intensified, focusing on plant-derived substances, particularly fruits, due to their rich phytochemical composition and gastroprotective potential (Kumar et al. 2022; Paradee et al. 2021).

In addition to their long-standing use in human nutrition, various fruits have been widely employed in traditional medicine across different cultures for the treatment of gastrointestinal disorders (Prazeres et al. 2019). For instance, the use of quince (*Cydonia oblonga*) is documented in Persian medicine for the relief of gastric ulcers, whereas *Phoenix dactylifera* (date palm) is traditionally used in the Middle East to promote digestive health (Hussein et al. 2023; Parvan et al. 2017). These ethnomedical practices reflect empirical knowledge accumulated over generations and have sparked scientific interest in validating such effects (Si et al. 2020). From the perspective of modern pharmacology, fruits offer relevant advantages, including a high diversity of bioactive compounds, low toxicity, affordability, and availability across different geographical regions, making them promising candidates for the development of safer and more effective gastroprotective therapies (Karasawa and Mohan 2018).

Various fruits are traditionally used in folk medicine for the relief of intestinal conditions, serving as a source of bioactive compounds such as flavonoids, terpenes, alkaloids, and phenolic acids, which exhibit antioxidant, anti-inflammatory, and gastroprotective activities (Tanyeli et al. 2023; Toktay et al. 2022). Despite traditional use and advances in understanding their properties, many studies have already investigated the molecular mechanisms involved in the gastrointestinal protection conferred by fruits (Jeon et al. 2022; Liu et al. 2024; Tan et al. 2023); however, there is still a need for a more integrated and consolidated view of these biological pathways.

Understanding the mechanisms of action and cellular signaling processes is essential for comprehending how the bioactive compounds in fruits exert their gastroprotective functions (Li et al. 2023). Cellular signaling, in turn, involves communication between cells through a complex network of chemical and molecular signals, which regulate responses such as inflammation and tissue regeneration (Hellenbrand et al. 2021). By studying these pathways, it is possible to identify specific therapeutic targets and enhance the development of more effective treatments.

This systematic review aims to explore and compile the mechanisms of action involved in the gastroprotective response of different fruits, seeking to provide a comprehensive view of the activated biological pathways, such as the modulation of inflammatory mediators, the preservation of mucosal barrier integrity, and the neutralization of free radicals. By integrating scientific findings, it is hoped to contribute to the development of new treatments on the basis of natural compounds, with potential for use in both the prevention and treatment of diseases affecting the gastrointestinal tract.

TABLE 1 | Databases used in the study and association of descriptors utilized.

Database	Associations
Scopus, PubMed, and Web of Science	*"Fruits and gastroprotective effect"*; *"Fruits and gastroprotective activity"*; *"Fruits and gastric mechanism of action"*; *"Fruits and gastric ulcer therapy"; "Fruits and pharmacological effect"*; *"Fruits and medicinal use"*; *"Fruits and pharmacological"*.

2 | Materials and Methods

2.1 | Search Strategy

The systematic review was conducted according to PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). It consists of a checklist of 27 items and a flow diagram that guides the research and selection of articles in four stages—identification, selection, eligibility, and inclusion—so that authors can contribute to the quality and reliability of the review in question.

The study was guided by the following question: "What are the mechanisms of action involved in the gastroprotective response of fruits?" The articles mentioned in the review were publications available from the first publication up to October 2024. For this research, the databases used were Scopus, PubMed, and Web of Science. The descriptors used, as well as the combinations adopted, are presented in Table 1.

The inclusion and exclusion criteria were applied across all consulted databases. Inclusion criteria: articles published in full text in English that address the subject through the association of the aforementioned terms. Exclusion criteria: duplicate articles, comparative studies, inconclusive or questionable studies. After applying the search criteria, a certification of the selected productions was conducted using a qualitative meta-synthesis approach.

The review protocol was registered and is available on PROSPERO under the number CRD42021281191. This registration ensured the transparency and replicability of the methodological process adopted, as well as facilitating comparison with other systematic reviews in the same field of study.

However, it is important to note that relying exclusively on previously published data may present limitations, such as methodological variability and potential publication bias. Future studies should include experimental research to complement and validate the findings discussed in this review.

2.2 | Selection of Studies

Two independent researchers (R.T.P. and L.Y.S.S.) were responsible for the article searches. The selection of articles was made through the reading of titles and abstracts, with the application of an evaluation form on the basis of eligibility criteria. Subsequently, the publications were assessed through complete reading. This step is essential to confirm the inclusion criterion. Any discrepancies were resolved between the two researchers. The selected articles were carefully reviewed to identify studies that would be included in the final sample of the study. A table was prepared with information on (1) family/species, (2) formulation/chemical composition, (3) dose/routes of administration, (4) injury-inducing agent, (5) evaluated mechanisms, (6) results found, and (7) reference.

2.3 | Methodological Quality Assessment/Risk of Bias (RoB) of the Studies

The RoB and methodological quality of the selected in vivo studies (non-human animals) were manually assessed by two researchers independently, using the RoB methodology from SYRCLE (Hooijmans et al. 2014). The final validation of the risk assessment was conducted by two independent researchers using the kappa index.

2.4 | Data Synthesis

The results were presented through a narrative synthesis, as it was not possible to perform a meta-analysis due to the high heterogeneity of the studies addressed in this review.

3 | Results and Discussion

3.1 | Data Extraction and Analysis

The initial search using descriptors associated with the Boolean operator "and" yielded a total of 2621 articles across the three databases utilized. After the initial screening, 360 articles were selected for full reading and identification of activities, with PubMed (107), Web of Science (173), and Scopus (80). It is noteworthy that, at this stage, duplicate articles (148) were excluded, totaling (212). After thorough reading and confirming the eligibility criteria of the studies, (164) articles were excluded. In the end, 48 articles were included in this review (Figure 1). The information from each study is highlighted in Table 2.

Among the highlighted species are pitaya (*Hylocereus polyrhizus*), date palm (*Phoenix dactylifera*), coriander (*Coriandrum sativum*), bael fruit (*Aegle marmelos*), blueberry (*Vaccinium corymbosum*), passion fruit (*Passiflora edulis*), hog plum (*Spondias mombin*), blackberry (*Morus nigra*), Himalayan blackberry (*Rubus niveus*), quince (*Cydonia oblonga*), black nightshade (*Solanum nigrum*), chokeberry (*Aronia melanocarpa*), golden kiwi (*Actinidia chinensis*), doum palm (*Hyphaene thebaica*), garcinia (*Garcinia cowa, Garcinia indica*, and *Garcinia cambogia*), corryocactus (*Corryocactus brevistylus*), Brazilian ironwood (*Libidibia ferrea*), oak (*Quercus* spp.), cucumber (*Cucumis sativus*), pointed gourd (*Trichosanthes dioica*), camellia (*Camellia japonica*), Chinese quince (*Pseudocydonia sinensis*), star apple (*Chrysophyllum cainito*), guabiroba (*Campomanesia reitziana*), pomegranate (*Punica granatum*), Chinese gooseberry (*Schisandra chinensis*), Manila tamarind (*Pithecellobium dulce*), aloe vera (*Aloe barbadensis*), spiny gourd (*Momordica dioica*), cordia (*Cordia myxa*), lemon (*Citrus lemon*), sweet orange (*Citrus sinensis*), naranjilla (*Solanum paniculatum*), Indian gooseberry (*Emblica officinalis*), cluster fig (*Ficus glomerata*), winter melon (*Benincasa hispida*), acacia (*Acacia nilotica*), cannonball mangrove (*Xylocarpus granatum*), pequi (*Caryocar coriaceum*), long pepper (*Piper tuberculatum*), black cardamom (*Amomum subulatum*), and noni (*Morinda citrifolia*). The diversity of these species highlights the vast bioactive potential found in both native and exotic fruits, reinforcing their relevance for future research in the field of gastroprotection.

Regarding the botanical aspects, the families of the identified species were Arecaceae ($n = 3$), Anacardiaceae ($n = 1$), Boraginaceae ($n = 1$), Clusiaceae ($n = 3$), Cucurbitaceae ($n = 4$), Cactaceae ($n = 3$), Ericaceae ($n = 1$), Euphorbiaceae ($n = 1$), Fagaceae ($n = 1$), Fabaceae ($n = 4$), Meliaceae ($n = 1$), Mimosoideae ($n = 1$), Myrtaceae ($n = 1$), Moraceae ($n = 2$), Oleaceae ($n = 1$), Passifloraceae ($n = 1$), Piperaceae ($n = 1$), Punicaceae ($n = 1$), Rosaceae ($n = 5$), Rutaceae ($n = 4$), Sapotaceae ($n = 1$), Solanaceae ($n = 1$), Schisandraceae ($n = 1$), Theaceae ($n = 1$), Xanthorrhoeaceae ($n = 1$), Zingiberaceae ($n = 1$), and Rubiaceae/Apiaceae/Rutaceae ($n = 1$). The last three families (Rubiaceae, Apiaceae, and Rutaceae) correspond to a species resulting from the hybridization of three different species.

The tested formulations included methanolic, hydroalcoholic, ethanolic, aqueous, and hexane extracts, as well as dry and crude extracts, fresh juices, soluble fibers, jellies, oils, and fractions of various natures. Regarding the chemical composition of the analyzed fruits, when specified, the main compounds highlighted were polyphenols, followed by alkaloids, terpenes, flavonoids, tannins, saponins, glycosides, steroids, butenolides, anthocyanins, carboxylic acids, and carbohydrates. Some studies only mentioned the classes of compounds, whereas others identified specific constituents.

Regarding the years of publication, the highest number of studies was between 2012, 2018, and 2017 ($n = 5$ for each). Concerning the routes of administration used in the tests, most opted for oral ($n = 48$), oral and intraperitoneal ($n = 2$), or intragastric ($n = 1$). It is important to note that some studies used more than one route.

The mechanisms of action evaluated in the selected studies were enzymatic antioxidant system defenses, non-enzymatic antioxidant system defenses, pro-inflammatory cytokines, prostaglandins, nitric oxide, H^+/K^+ ATPase, pepsin, mucin, gastrin, α_2 receptors, histamine receptors, and muscarinic receptors, as well as the expression of cell signaling markers such as p-EGFR, nuclear factor kappa B (NF-κB), Bax, cleaved-caspase-3, cyto-C, and cleaved-PARP. Most studies assessed and confirmed the possible involvement of more than one of the mentioned mechanisms (Figures 2 and 3). Furthermore, the mechanisms that appeared most evident among the identified articles were detailed, along with the species associated with each of them.

TABLE 2 | Description of studies conducted with fruits considering their mechanisms of action.

Family/ Species	Formulation/ Chemical composition	Dose/ Concentration/ Route of Administration	Inducer of lesions agent	Assessed mechanisms	Results	References
Cactaceae *Hylocereus polyrhizus*	Extract N.r.	500 and 1000 mg/kg v.o.	Indomethacin	MDA, GSH, Caspase 3, BAX, COX-1, and COX-2	The fruit extract was protected against indomethacin-induced ulcer damage by reduced levels of MDA, increased levels of GSH, and inhibition of Caspase 3, BAX, and Cox-2, along with activation of Cox-1	Toktay et al. (2022)
Arecaceae *Phoenix dactylifera* L. Cv.	Extract Phenolic components, tannins, and flavonoids	8 mL/kg v.o.	EtOH	Gastrin and GSH	Date extracts (fruit, seed, and combination) reduced gastric ulceration and protected against the effects of ethanol on gastrin, glutathione, and gastric mucus, possibly due to their antioxidant properties	Hussein et al. (2023)
Rubiaceae, Apiaceae, and Rutaceae *Morinda citrifolia* L., *Coriandrum sativum* L., and *Aegle marmelos* (L.)	Extract from the three species (Pikad Tri-phol-sa-mut-than—TS) Phenolic components and flavonoids	150, 300, and 600 mg/kg v.o.	Stress, indomethacin EtOH, and HCl	Mucus of the gastric wall	Our findings suggest that TS has gastric anti-ulcer effects, related to the increased formation of gastric mucus and its antioxidant and anti-apoptotic properties	Tan et al. (2023)
Actinidiaceae *Actinidia chinensis* L.	Fermented gold kiwi extract (FGK) Flavonoids	50, 125, and 250 mg/kg v.o.	HCl/EtOH	iNOS, COX-2, IL-6, TNF-α, and prostaglandin E2 (PGE_2)	The FGK increased antioxidant activity, and the secretion of the defensive factor PGE_2 decreased the expression of inflammatory factors (iNOS, COX-2, TNF-α, and IL-6) and inhibited gastric acid secretion	Jeon et al. (2022)
Arecaceae *Hyphaene thebaica* Mart. (Doum)	Ethanolic extract N.r.	250 and 500 mg/kg v.o.	EtOH	Lipid peroxidation, non-protein thiol, superoxide dismutase (SOD), nitric oxide, and Bax and Bcl-2	These properties were observed to be mediated by the modulation of oxidative stress. Additionally, it modulated the proteins Bcl-2 and Bax and inhibited apoptosis	Taha et al. (2022)
Clusiaceae *Garcinia cowa* Roxb. ex Choisy	Hydroalcoholic extract Gallic acid, amentoflavone, polyphenol, and flavonoid	200 and 400 mg/kg v.o.	EtOH	Mucus of the gastric wall, MDA, SOD, and NP-SH	The pre-treatment restored gastric mucus and NP-SH, reduced the microvascular permeability of Evans Blue, and increased oxidative enzyme activity, reducing MDA and increasing SOD, indicating a protective and antioxidant effect	Gupta et al. (2021)

(Continues)

TABLE 2 | (Continued)

Family/ Species	Formulation/ Chemical composition	Dose/ Concentration/ Route of Administration	Inducer of lesions agent	Assessed mechanisms	Results	References
Cactaceae *Corryocactus brevistylus* (K. Schum. ex Vaupel) Britton & Rose	In natura epicarp and pulp Malic acid, citric acid, ascorbic acid, rutin, and quercetin	10, 25, 50, and 100 mg/kg v.o.	HCl/EtOH	NO, PGs, and NP-SH	The effect induced by the extract at 50 mg/kg was reversed by indomethacin and *N*-ethylmaleimide but not by NG-nitro-L-arginine, suggesting the involvement of prostaglandins and sulfhydryl compounds in the gastroprotective effect promoted by the extract	Areche et al. (2020)
Ericaceae *Vaccinium corymbosum* L. and *Vaccinium darrowii* Camp.	Crude extract obtained using NADES and fractions of the extract Anthocyanins	10 mg/kg v.o.	EtOH	GSH, GSSG, GR, GST, levels of nitrite and nitrate (Nox), MPO, the activity of Cu/Zn SOD, and Nrf2	The pre-treatment with ce reduced glutathione depletion and the inflammatory response (mpo). The gastroprotective properties were associated with the mitigation of oxidative stress and neutrophil infiltration	da Silva et al. (2020)
Oleaceae *Schrebera arborea*	Hexane extract and ethanolic extract Gallic acid, catechin, caffeic acid, *p*-coumaric acid, ferulic acid, rutin, apigenin 7-glucoside, quercetin, kaempferol, isorhamnetin, and amentoflavone	50, 100, or 150 mg/kg v.o.	EtOH; indomethacin	SOD, GSH, CAT, and MDA	It inhibited ethanol- and indomethacin-induced lesions. It reduced the level of MDA. It proved to be effective in the gastroprotective effect by increasing the activity of antioxidant enzymes	Sofidiya et al. (2020)
Schisandraceae *Schisandra chinensis* (Turcz.) Baill.	Ethanolic extract N.r.	80, 160, and 320 mg/kg v.o.	EtOH	MDA, SOD, and levels of TNF-α and IL-1β	The extract significantly reduced the ulcer index, increasing the levels of SOD, decreasing the levels of MDA, and reducing the plasma levels of TNF-α and IL-1β	Si et al. (2020)
Fabaceae *Libidibia ferrea* Mart. ex Tul.	Dry extract Gallic acid and ellagic acid	50, 100, 200, and 400 mg/kg v.o.	Indomethacin, EtOH, and EtOH/HCl	MDA, determination of mucus concentration, pyloric ligation, and NO and –SH; *Helicobacter pylori*	The extract inhibited indomethacin-induced lesions and reduced gastric secretion and H^+ concentration, with protection dependent on sulfhydryl (–SH) compounds. In the chronic model, it reduced lesion area and showed anti-*H. pylori* antibodies	Prazeres et al. (2019)

(Continues)

TABLE 2 | (Continued)

Family/ Species	Formulation/ Chemical composition	Dose/ Concentration/ Route of Administration	Inducer of lesions agent	Assessed mechanisms	Results	References
Passifloraceae *Passiflora edulis* f. flavicarpa	Soluble fiber N.r.	0, 1, 1, and 10 mg/kg v.o. and intraperitoneal (i.p.)	EtOH	Measurement of the gastric wall mucus; reduced GSH levels	The pre-treatment significantly reduced ethanol-induced gastric ulcer lesions and prevented the depletion of GSH levels and mucus in the gastric wall	Abboud et al. (2019)
Anacardiaceae *Spondias mombin* L	Fresh juice Epicatechin and quercetin (polyphenol and flavonoid)	25%, 50%, and 100% (10 mL/kg) v.o.	EtOH, indomethacin, and acetic acid	–SH, PGs; pyloric ligation; determination of mucus adhered to the mucosa	It reduced ethanol- and indomethacin-induced lesions, gastric content, and acidity, restoring mucus levels in glandular cells and increasing cell proliferation	Brito et al. (2018)
Fagaceae *Carvalho* (*Jaft*)	Aqueous extract N.r.	250, 500, and 750 mg/kg v.o.	Stress-induced lesions	NO and MDA	The average thickness of the mucous glands in the treated groups did not significantly decrease compared to the control. However, NO and MDA levels in the control group decreased compared to the treated groups. The extract exhibits biological properties, such as antioxidant effects and inhibition of lipid oxidation	Barmak et al. (2018)
Cucurbitaceae *Trichosanthes dioica*	Ethanolic extract N.r.	100, 200, and 400 mg/kg v.o.	Aspirin Acetic acid EtOH	SOD, CAT, lipid peroxidase (LPO), and pyloric ligation	Preliminary results indicate that the extract reduces gastric secretion associated with damage from reactive oxygen species (ROS), acid, and pepsin. An increase in LPO and a decrease in CAT were observed	Kumar et al. (2018)
Rosaceae *Pseudocydonia sinensis* Thouin	Jelly N.r.	1.5 mL diluted jelly Intragastric	HCl/EtOH	TNF-α and MPO	The jelly protected gastric tissues against HCl/ethanol-induced gastric injury, as demonstrated by the reduction in the gastric injury index and levels of TNF-α	Hamauzu et al. (2018)

(Continues)

TABLE 2 | (Continued)

Family/ Species	Formulation/ Chemical composition	Dose/ Concentration/ Route of Administration	Inducer of lesions agent	Assessed mechanisms	Results	References
Sapotaceae *Chrysophyllum cainito* L.	Methanolic extract of peels (MEPe) and pulp (MEPu) MEPe: myricitrin, catechin, quercitrin, quercetin, and gallic acid. MEPu: polyphenol flavonoid	1–30 mg/kg v.o.	EtOH; indomethacin and HCl/EtOH	Pyloric ligation, determination of mucus, adhered to the mucosa, and NO and SH	MEPe and MEPu protected against ethanol/HCl- and indomethacin-induced lesions. MEPe effect was inhibited by NEM, glibenclamide, yohimbine, and indomethacin; MEPU effect was reduced by NEM and L-NAME. Neither extract affected gastric acid secretion	da Rosa et al. (2019)
Myrtaceae *Campomanesia reitziana*	Methanolic extract Dimethyl cardamonin chalcone	MECR (30, 100, and 300 mg/kg) DMC (1 and 3 mg/kg) v.o.	HCl/EtOH	GSH, lipid peroxides (LOOH), SOD, and CAT	The pretreatment with MECR reduced gastric lesions. Additionally, the extract increased mucin content and SOD activity while decreasing lipid peroxide levels. However, MECR did not prevent the depletion of reduced glutathione or the reduction in catalase (CAT) activity	de Oliveira Cabral et al. (2017)
Moraceae and Rosaceae *Morus nigra* L. *Rubus niveus*	Methanolic extract N.r.	MEMN (30–300 mg/kg) and MERN (10–300 mg/kg) v.o.	HCl/EtOH	Lipid hydroperoxides, reduced glutathione levels, and H^+/K^+ ATPase activity	MEMN reduced the ulcer area and increased gastric mucin levels. The antioxidant effects of the extracts were evidenced by the reduction in lipid peroxides and an increase in reduced glutathione levels in the gastric mucosa. However, MEMN and MERN did not alter H^+/K^+-ATPase	Nesello et al. (2017)
Theaceae *Camellia japonica*	Ethanolic extract Gallic acid and rutin, flavonoid, and polyphenol	100 mg/kg v.o.	HCl/EtOH	NO, ROS, MDA, and qPCR	Reduced lipid peroxidation and increased NO production. Downregulated expression of cytokines, COX-2, and inflammatory enzymes, with inhibition of MAPK phosphorylation, NF-κB activation, and IκBα degradation in gastric mucosa	Akanda; Park (2017)
Rosaceae *Cydonia oblonga* Miller	Aqueous extract (QAE) Hydroalcoholic extract (QHE) N.r.	200, 500, and 800 mg/kg v.o.	Indomethacin	MPO and Pepsin measurement	The protective effect of QAE and QHE on gastric ulcer was achieved by mitigating offensive factors, including decreased gastric acid secretion and pepsin activity, while enhancing the protective factors of gastric mucus, including antioxidant capacity	Parvan et al. (2017)

(Continues)

TABLE 2 | (Continued)

Family/ Species	Formulation/ Chemical composition	Dose/ Concentration/ Route of Administration	Inducer of lesions agent	Assessed mechanisms	Results	References
Rutaceae *Citrus sinensis* L.	Extract aqueous Hesperidin, quercetin, and flavonoids	100, 200, and 400 mg/kg v.o.	EtOH	COX-2, TNF-α, MDA, –SH, SOD, CAT, and GPx	Improvement in the levels of oxidative stress markers such as MDA and H_2O_2, increased pro-inflammatory cytokine (TNF-α level), as well as COX-2 expression in the ethanol group. Significant depletion of enzymatic and non-enzymatic antioxidants, such as GPx, SOD, CAT, and –SH, was associated with severe histopathological damage	Selmi et al. (2017)
Rutaceae *A. marmelos*	Methanolic extract N.r.	(MEAM): 25, 50, 100, 250, and 500 mg/kg v.o.	*H. pylori* and Lipopolysaccharide (HP-LPS)	SOD, CAT, GPx, GR, GSH, LPO, GSTs, vitamin E, and vitamin C	Treatment prevented the decrease of enzymatic (SOD, CAT, GPx, GR, and GST) and non-enzymatic (GSH, vitamin C, and vitamin E) antioxidants after HP-LPS induction	Ramakrishna et al. (2015)
Fabaceae *Pithecellobium dulce*	Hydroalcoholic extract N.r.	200 mg/kg v.o.	60% ethanol and cysteamine hydrochloride	H^+, K^+ -ATPase β, expression of MUC6 and MUC2	The treatments negatively regulated the expression of the H^+, K^+-ATPase β subunit and gastroprotective mucins, and MUC6 and MUC2, in the stomach and duodenum	Megala and Devaraju (2015)
Fabaceae *P. dulce* (Roxb.) Benth	Hydroalcoholic extract (HAEPD) N.r.	100, 200, and 500 mg/kg v.o.	Cysteamine	SOD, GATO, GSHe, and GPx	Significant reduction in ulcer scores, comparable to those of rats treated with ranitidine. The coadministration of HAEPD reduced the level of thiobarbituric acid and restored the levels of glycoproteins and enzymatic and non-enzymatic antioxidants	Megala and Geetha (2015)
Xanthorrhoeaceae *Aloe barbadensis* Mill.	Juices (in natura) N.r.	20.0 mL/kg N.r.	Ethanol 40%	Determination of total acidity in gastric fluid, serum alkaline phosphatase assay, GSH, SOD, and lipid peroxidation	The treatment decreased acid secretion, reduced proteins and carbohydrates in gastric fluid, increased defense factors (SOD and GSH), and normalized hemoglobin levels and red and white blood cell counts	Gopinathan and Rameela (2014)

(Continues)

TABLE 2 | (Continued)

Family/ Species	Formulation/ Chemical composition	Dose/ Concentration/ Route of Administration	Inducer of lesions agent	Assessed mechanisms	Results	References
Clusiaceae *Garcinia indica* Choisy	Aqueous extract (GIE) N.r.	400 and 800 mg/kg v.o.	Absolute ethanol, aspirin, and histamine	SOD, CAT, GPx, GR, GSH, and lipid peroxidation	It reduced the ulcer index in a dose-dependent manner in three distinct models. The GIE, at both doses, demonstrated significant antioxidant activity by reducing elevated levels of MDA associated with ulcers and restoring levels of GSH, SOD, CAT, GPx, and GR	Panda and Khambat (2014)
Piperaceae *Piper tuberculatum* Jacq.	Dichloromethane fraction of the fruit of *P. tuberculatum* Piplartine and alkaloid	DFPT (10, 30, and 100 mg/kg or 1, 3, and 10 mg/kg) and piplartine (4.5 mg/kg) i.p. or v.o.	EtOH	Mucin concentration and GSH levels	The DFPT provided gastroprotection against acute lesions induced by ethanol, possibly due to the maintenance of GSH levels in the gastric mucosa. Furthermore, the DFPT reduced both basal gastric acid secretion and that stimulated by pentagastrin	Burci et al. (2013)
Fabaceae *P. dulce*	Hydroalcoholic extract N.r.	100, 200, and 500 mg/kg v.o.	AA, SHR, and EtOH	Gastric fluid volume, pH, and acidity; pepsin activities; H^+, K^+-ATPase; MPO; content of mucin, nucleic acids, glycoproteins, and PGE_2	The treatments increased defense factors such as prostaglandin and mucin. They reduced offensive factors, such as acid secretion and pepsin activity	Megala and Geetha (2012)
Cucurbitaceae *Cucumis sativus*	Aqueous extract Flavonoids, polyphenols, alkaloids, glycosides, steroids, and tannins	250, 500, and 1000 mg/kg v.o.	EtOH, indomethacin, and AA	Pyloric ligation, LPO, SOD, CAT, ulcer healing, estimation of free radical generation, estimation of total proteins, total carbohydrates, total hexoses, hexosamines, fucose, and sialic acid	It reduced lesions in the indomethacin and pyloric ligation models, significantly increased antioxidant activities, reduced ulcers induced by acetic acid, demonstrating healing capacity, and exhibited effective gastroprotective properties	Sharma et al. (2012)

(Continues)

TABLE 2 | (Continued)

Family/ Species	Formulation/ Chemical composition	Dose/ Concentration/ Route of Administration	Inducer of lesions agent	Assessed mechanisms	Results	References
Mimosoideae *Acacia nilotica* Subsp Indica	Ethanolic, hydroethanolic, and aqueous extract Alkaloids, saponins, flavonoids, tannins, and carbohydrates	50, 100, and 200 mg/kg v.o.	Swimming stress and indometacin	Gastric acid secretion, pH, free acidity, total acidity, ulcer index, mucin content, and antioxidant studies. MPO, TNF-α, and lipid peroxidation	The hydroethanolic extract showed antiulcer activity in pyloric ligation, stress, and NSAID-induced ulcer models, with significant mucoprotection	Bansal and Goel (2012)
Cactaceae *Opuntia ficus* indica var. saboten	Fruit juice N.r.	OFSM (800 and 1600 mg/kg) v.o.	Water immersion restraint stress (WIRS)	MPO, TNF-α, and lipid peroxidation	OFSM reduced stress-induced lesions and prevented the decrease of gastric mucus. OFSM suppressed increases in TNF-α and myeloperoxidase in the gastric mucosa induced by WIRS	Kim et al. (2012)
Rutaceae *A. marmelos*	Aqueous extract N.r.	250 mg/kg v.o.	Aspirin	Aspartate aminotransferase (AST), alanine aminotransferase (ALT), CAT, SOD, reduced glutathione (GSH), and LPO	Aspirin increased IU, AST, ALT, ALP, and LPO and decreased MT, SOD, CAT, and GSH. Pretreatment with the extract reversed these effects, suggesting gastro-duodenal protection via antioxidant mechanisms	Das and Roy (2012)
Cucurbitaceae *Momordica dioica* Roxb.	Hydroalcoholic extract N.r	100, 200, and 400 mg/kg v.o.	EtOH and cold restraint stress	Gastric mucus, SOD, LPO, pyloric ligation, CAT, and H^+-K^+ ATPase	Pretreatment reduced gastric lesions, increased gastric wall mucus, LPO, and SOD, and reduced gastric volume; it also affected acid production and increased pH in the pyloric ligation-induced ulcer model. The possible mechanism of the antiulcer activity of the fruits may be attributed to their antioxidant and free radical scavenging activity	Vijayakum et al. (2011)
Boraginaceae *Cordia myxa*	Ethanolic extract Glycosides, flavonoids, saponins, terpenes, alkaloids, and phenolic acids	CME: 125 mg/kg v.o.	Indomethacin	MDA, nitric oxide, catalase activity, PGE_2, and TNF-α	CME pretreatment reduced MDA and TNFα and increased mucin, CAT, NO, and PGE_2 levels, suggesting protection against indomethacin-induced ulcers via antioxidant and mucin-enhancing effects	Abdallah et al. (2011)

(Continues)

TABLE 2 | (Continued)

Family/ Species	Formulation/ Chemical composition	Dose/ Concentration/ Route of Administration	Inducer of lesions agent	Assessed mechanisms	Results	References
Rutaceae *Citrus lemon* (CL)	Essential oil CL Limonene and β-pinene	50, 100, 250, 500, and 1000 mg/kg v.o.	EtOH and indomethacin	GSH, NO, SH, PGE_2, and HSP70 (stress-responsive protein)	CL provided 100% gastroprotection, including in the indomethacin model. Its effect was linked to increased mucus, HSP-70, and PGE_2 and was reduced by NO synthase inhibitor and SH blocker	Rozza et al. (2011)
Meliaceae *Xylocarpus granatum*	Ethanolic extract Chloroform fraction (Fr-CHCl(3)) N.r.	200, 400, and 800 mg/kg and 10, 20, and 40 mg/kg v.o.	Cold restraint, aspirin, alcohol, pyloric ligation, and histamine	Antisecretory activity	Fr-$CHCl_3$ exhibited antiulcer activity in various models, significantly reducing free acidity and total acidity while increasing mucin secretion. Its antiulcerogenic activity may be attributed to its antisecretory action and the strengthening of gastric defenses	Lakshmi et al. (2010)
Caryocaraceae *Caryocar coriaceum* Wittm	Pulp oil N.r.	200 and 400 mg/kg v.o.	Absolute ethanol and aspirin	α_2-receptors, prostaglandins, nitric oxide, and K^+ ATP channels	The oil significantly reduced ethanol- and aspirin-induced gastric lesions, acting via α_2 receptors, prostaglandins, nitric oxide, and K^+ ATP channels	da Silva Quirino et al. (2009)
Cucurbitaceae *Benincasa hispida* (Thunb.) Cogn.	Methanol and petroleum (PE) ether extracts of the fruits N.r.	300 mg/kg v.o.	Cold (stress-induced confinement) and EtOH	Pyloric ligation, vascular permeability, mucoprotective parameters, MDA, SOD, and CAT	Reduced vascular permeability and MDA levels, with increased CAT. Gastroprotection may involve antioxidant effects and strengthening of the mucosal barrier	Rachchh; Jain (2008)
Moraceae *Ficus glomerata*	Juice N.r.	FGE: 0.5, 1.0, and 2.0 mL equivalent a 240, 480, and 960 mg/kg v.o.	Aspirin, EtOH, and stress	Pyloric ligation and mucus secretion	FGE dose-dependently reduced ulcer index in pyloric ligation, ethanol, and stress models. Its effect involved inhibition of lipid peroxidation and H^+/K^+-ATPase, reduction of SOD, and increased CAT, likely due to phenolic compounds and gastric defense factors	Rao et al. (2008)
Rosaceae *Solanum nigrum* (L.)	Fruit extract Alkaloids, carbohydrates, steroids, anthocyanins, saponins, tannins, and polyphenols	200 and 400 mg/kg v.o.	Stress induced by cold restraint, indomethacin, EtOH, and acetic acid	Concentration of the hormone gastrin, pyloric ligation, determination of H^+, and K^+-ATPase	It accelerated the healing of ulcers and reduced ulcers by decreasing gastrin secretion; the extract from *S. nigrum* (L.) fruits has effective gastroprotective effects	Jainu and Devi (2006)

(Continues)

TABLE 2 | (Continued)

Family/ Species	Formulation/ Chemical composition	Dose/ Concentration/ Route of Administration	Inducer of lesions agent	Assessed mechanisms	Results	References
Rosaceae *Aronia melanocarpa* Elliot	Filtered and pasteurized juices N.r.	5, 10, or 20 mL/kg v.o.	Indomethacin	MDA, GSH, and GSSG	It reduced gastric mucosal injury induced by indometacin, showing morphometric and histomorphological signs. A possible mechanism of ulcer protection by AMFJ is an anti-secretory effect. AMFJ did not significantly influence the levels of GSH and GSSG	Valcheva-Kuzmanova et al. (2005)
Arecaceae *P. dactylifera* L	Aqueous and ethanolic extracts N.r.	4 mL/kg v.o.	EtOH	Plasma gastrin concentrations; histamine and mucus	Aqueous and ethanolic extracts reduced ethanol-induced increases in histamine and gastrin and prevented mucin depletion; the undialyzed ethanolic extract showed the greatest effect, suggesting protection against ethanol-induced ulcers	Al-Qarawi et al. (2005)
Punicaceae *Punica granatum* L.	Methanolic extract a 70% N.r.	250 and 500 mg/kg v.o.	Aspirin and EtOH	SOD, GSH, and GPx	The administration of the extract showed a significant percentage of inhibition in gastric ulceration induced by aspirin and ethanol. The results of this investigation revealed the gastroprotective activity of the extract through the evaluated antioxidant mechanisms	Ajaikumar et al. (2005)
Clusiaceae *Garcinia cambogia* (Gaertn.) Desr.	Extract N.r.	0.5, 1, and l.5 mg/kg v.o.	HCI/EtOH	LPO, SOD, CAT, GSH_Px, and GST	The extract protected the gastric mucosa by reducing the volume and acidity of gastric juice, maintaining almost normal levels of lipid peroxidation, antioxidant enzyme activity, and levels of proteins and glycoproteins in the ulcerated mucosa and gastric juice	Mahendran et al. (2002)
Solanaceae *Solanum paniculatum* L.	Aqueous extract N.r.	0.5 and 2.0 g/kg v.o.	Stress and indomethacin	Histamine and Muscarinic	The fruit extracts stimulated gastric acid secretion. The stimulatory effect of the fruit extract was inhibited by pretreatment with atropine but not with ranitidine, suggesting that the fruit extract activates the muscarinic pathway for gastric acid secretion	Mesia-Vela et al. (2002)

(Continues)

TABLE 2 | (Continued)

Family/ Species	Formulation/ Chemical composition	Dose/ Concentration/ Route of Administration	Inducer of lesions agent	Assessed mechanisms	Results	References
Zingiberaceae *Amomum subulatum* Roxb.	Crude methanolic extract, fractions soluble in PE, ethyl acetate (EA), and methanol (MM). Fraction insoluble in methanol (MITM) and essential oil (1%) N.r.	Methanolic extract (430, 860, 1720 mg/kg), PE (200 mg/kg), EA (200 and 400 mg/kg), and MITM (860 mg/kg) v.o.	Aspirin and EtOH	Pyloric ligation, mucus of the gastric wall, and pepsin concentration in gastric juice	The EA fraction increased mucus production in the gastric wall and demonstrated direct protection of the mucosal barrier. The reduction in gastric motility by the essential oil and PE ether fractions suggests a gastroprotective action of the tested drug	Jafri et al. (2001)
Euphorbiaceae *Emblica officinalis* Gaertn	Juice N.r.	240, 480, and 960 mg/kg v.o.	Aspirin, EtOH, and stress	Pyloric ligation; mucus in the gastric wall	EOJ decreased acid and pepsin secretion, increased mucin and glycoprotein content, and reduced cell loss, indicating enhanced mucosal protection through modulation of aggressive and protective factors	Rao et al. (2001)

Abbreviation: N.r., not reported. v.o., oral route

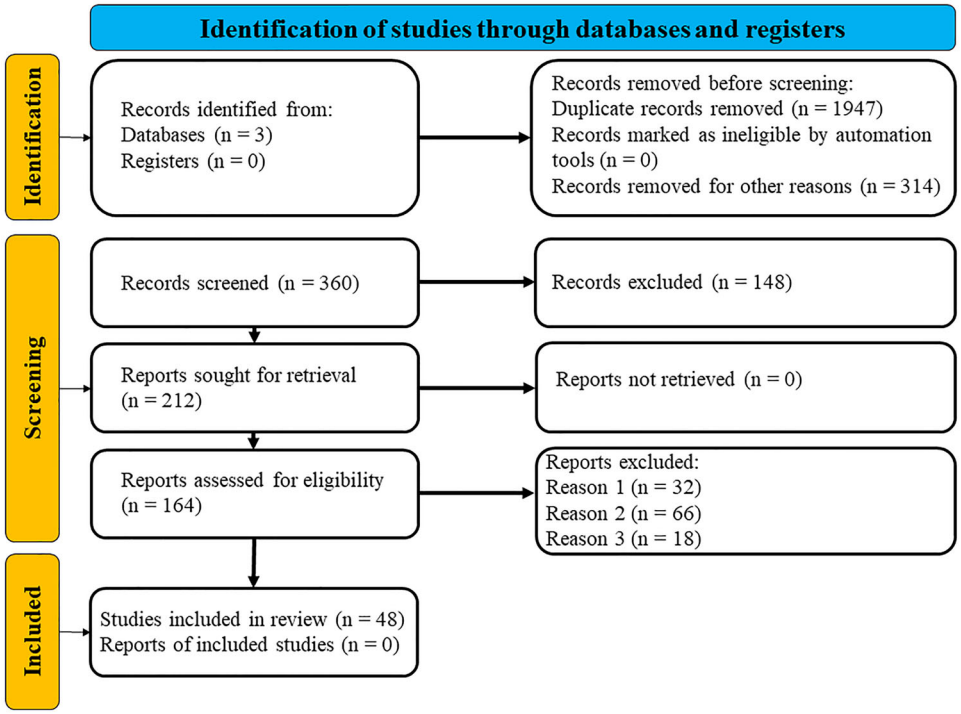


FIGURE 1 | Flowchart detailing the literature search according to the PRISMA statement. Reason 1: Articles with unavailable full text. Reason 2: Articles presenting mixtures of compounds or addressing parts of the plant other than fruits. Reason 3: Articles not specifically dealing with fruits or that did not address the mechanism of action.

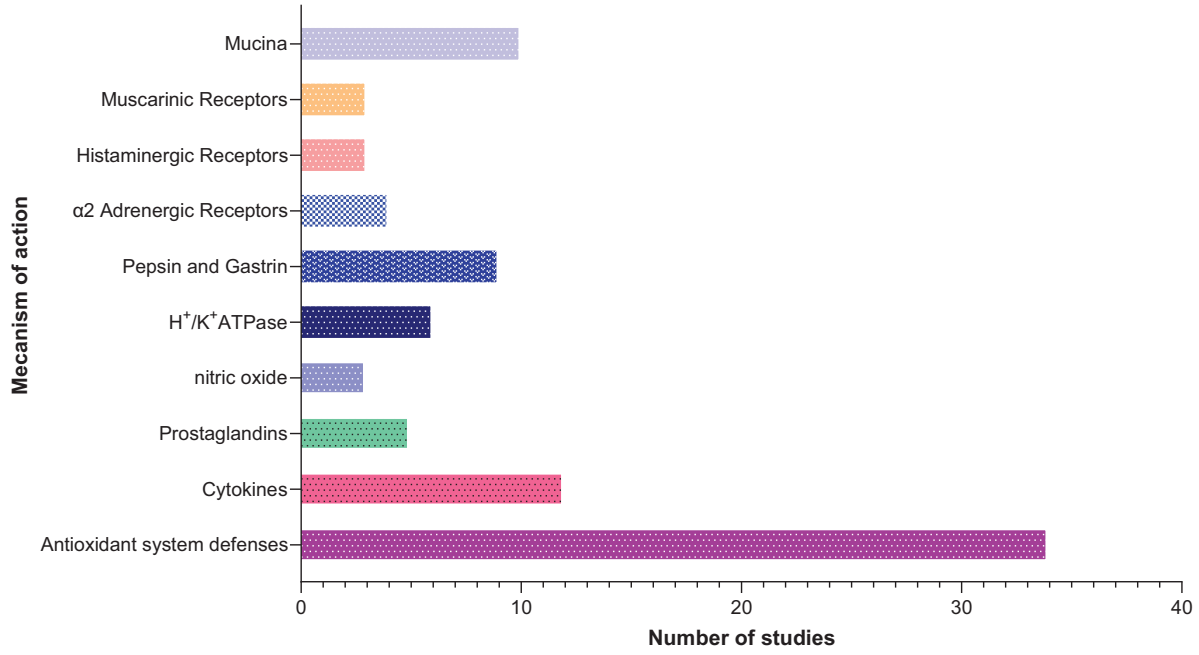


FIGURE 2 | Mechanisms of action involved in the gastroprotective response of the fruits analyzed in the study. Most species exhibited multiple mechanisms of action simultaneously.

3.2 | Methodological Quality/RoB of the Studies

To assess the methodological quality and RoB of the analyzed studies, the SYRCLE's RoB tool was used, which is based on the Cochrane RoB tool (Higgins 2011; Hooijmans et al. 2014), adapted for specific aspects of experimental studies involving non-human animals. This methodology assessed the RoB by addressing 10 questions, which include biases such as selection, performance, attrition, detection, and others (Hooijmans et al. 2014).

Some evidence suggests that the animal environment and experimental conditions, such as lighting, humidity, and temperature,

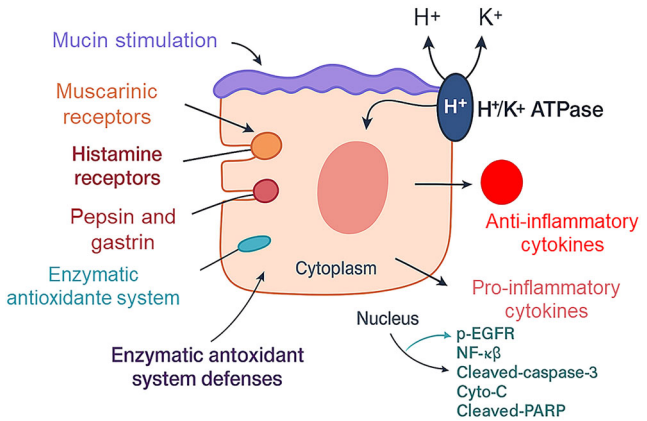


FIGURE 3 | Schematic illustration of the mechanisms of action involved in the gastroprotective response promoted by fruits in in vivo rodent models. According to the studies reviewed, gastroprotection occurs through multiple pathways, including stimulation of mucin production, modulation of muscarinic and histaminergic receptors, inhibition of the proton pump (H^+/K^+ ATPase), reduction of pepsin and gastrin activity, activation of enzymatic antioxidant defenses, and regulation of inflammatory mediators such as pro- and anti-inflammatory cytokines, in addition to the modulation of apoptosis-related proteins.

can influence study outcomes, as they affect behavior and biochemical responses (Claassen 2013; Hooijmans et al. 2014). Factors such as random group allocation and the use of blinded treatments are equally relevant to ensuring methodological quality. In this study, the articles were evaluated both qualitatively (Table 3) and quantitatively (Figure 4), ensuring the reproducibility of the adopted risk criteria. The initial classification was performed independently by two researchers (R.T.P. and L.Y.S.S.) with a kappa index of 0.793.

None of the in vivo studies included in this review demonstrated a low RoB. Out of a total of 48 studies, 33 exhibited a high RoB in at least one or two of the judgment questions. All studies presented an uncertain RoB. As shown in Figure 4, the analysis of in vivo experiments revealed that 8.5%, 33.8%, and 57.7% of the articles had a high, uncertain, and low RoB, respectively.

3.3 | Mechanisms of Action

3.3.1 | Enzymatic and Non-Enzymatic Antioxidant System Defenses

The protection of the gastric mucosa against oxidative damage is one of the main mechanisms involved in the gastroprotective effects of fruits. The production of reactive oxygen species (ROS) during inflammatory processes or due to the consumption of harmful substances, such as alcohol and non-steroidal anti-inflammatory drugs (NSAIDs), can lead to injury of gastric cells (Eddaikra and Eddaikra 2021; Ologundudu 2021). To combat this oxidative stress, the body employs antioxidant defenses that can be divided into two main categories: enzymatic and non-enzymatic (Włodarczyk et al. 2023).

The enzymatic antioxidant systems include enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) (Guemouri et al. 1991). These enzymes work synergistically to neutralize free radicals by converting ROS into less reactive or harmless forms (Gusti et al. 2021). SOD, for example, converts the superoxide anion into hydrogen peroxide, which is subsequently converted into water and oxygen by the action of CAT and GPx (Gusti et al. 2021). In this way, these enzymes protect the gastric mucosa from oxidative damage and help maintain cellular integrity (Vives-Bauza et al. 2007).

Non-enzymatic antioxidants, on the other hand, are bioactive compounds found in fruits, including vitamins (C and E), polyphenols, flavonoids, carotenoids, and phenolic compounds (Ashraf et al. 2019). These molecules act directly in neutralizing free radicals, either by donating electrons or by stabilizing these radicals (Balsano and Alisi 2009). Flavonoids, widely found in fruits, have been shown to be effective in modulating the activity of antioxidant enzymes and enhancing defense against ROS, thereby reducing inflammation and tissue damage (Rudenko et al. 2023).

The results of this review demonstrate that fruits from species, such as *H. polyrhizus*, *P. dactylifera*, *Prunus laurocerasus*, *H. thebaica*, *G. cowa*, *V. corymbosum*, *Vaccinium darrowii*, *S. arborea*, *S. chinensis*, *P. edulis* f. flavicarpa, *T. dioica*, *C. reitziana*, *M. nigra*, *R. niveus*, *C. sinensis*, *A. marmelos*, *P. dulce*, *A. barbadensis*, *G. indica*, *P. tuberculatum*, *C. sativus*, *B. hispida*, *P. granatum*, and *G. cambogia* are rich in antioxidant compounds, including flavonoids. These compounds have the ability to enhance enzymatic activity, playing a crucial role in the repair of the mucosa (Ivyna de Araújo Rêgo 2022).

3.3.2 | Cytokine Regulators

Inflammation plays a central role in the development of gastric lesions, especially in chronic conditions such as gastritis and peptic ulcers. During the inflammatory response, the immune system releases a series of inflammatory mediators, including pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 (Zhang and An 2007). These cytokines serve to recruit immune cells to the site of inflammation, increasing the production of inflammatory mediators, which results in tissue damage (Kany et al. 2019).

In the context of the gastric mucosa, the increase in pro-inflammatory cytokines is associated with the breakdown of the stomach's protective barriers, such as the production of mucus and bicarbonate. This makes the mucosa more vulnerable to the action of gastric acids and pepsin, facilitating the development of ulcers (Bockerstett and DiPaolo 2017). Some fruits, however, contain bioactive compounds that can modulate the release of pro-inflammatory cytokines, helping to control inflammation and promoting mucosal regeneration (Colombo et al. 2013).

Polyphenols, flavonoids, and other bioactive compounds found in fruits are capable of regulating the expression of inflammatory cytokines by inhibiting the activation of NF-κB, a key regulator of the inflammatory response (Choy et al. 2019). By inhibiting this

TABLE 3 | Summary of risk of bias.

References	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
Toktay et al. (2022)	−	+	?	+	?	?	+	?	+	+
Hussein et al. (2023)	+	+	?	+	?	+	+	?	+	+
Tan et al. (2023)	−	+	−	+	?	?	+	?	+	+
Jeon et al. (2022)	+	?	−	+	?	?	+	?	+	+
Taha et al. (2022)	+	+	+	+	?	?	+	?	+	+
Gupta et al. (2021)	+	+	+	+	?	+	+	?	+	+
Areche et al. (2020)	+	?	?	?	?	?	+	?	+	+
da Silva et al. (2020)	−	+	?	+	?	?	+	?	+	+
Sofidiya et al. (2020)	+	+	−	?	?	+	+	?	+	+
Si et al. (2020)	−	+	?	+	?	?	+	?	+	+
Prazeres et al. (2019)	+	+	−	?	?	?	+	?	+	?
Abboud et al. (2019)	+	+	?	+	?	?	+	−	+	+
Brito et al. (2018)	+	+	?	+	?	?	+	−	+	+
Barmak et al. (2018)	+	+	?	+	?	?	+	?	+	+
Kumar et al. (2018)	+	+	?	+	?	?	+	?	+	+
Hamauzu et al. (2018)	+	+	−	?	?	?	+	?	+	+
da Rosa et al. (2019)	+	+	?	+	?	?	+	?	+	+
de Oliveira Cabral et al. (2017)	+	+	−	?	?	?	+	?	+	?
Nesello et al. (2017)	+	+	?	+	?	?	+	−	+	+
Akanda; Park (2017)	+	+	?	+	?	?	+	−	+	+
Parvan et al. (2017)	+	+	?	+	?	?	+	?	+	+
Selmi et al. (2017)	+	+	?	+	?	?	+	?	+	+
Ramakrishna et al. (2015)	+	+	−	+	?	?	+	?	+	+
Megala and Devaraju (2015)	+	?	?	+	?	?	+	?	+	+
Megala and Geetha (2015)	+	+	−	+	?	?	+	?	+	?
Gopinathan and Rameela (2014)	+	+	?	+	?	?	+	−	+	+
Panda and Khambat (2014)	+	?	?	+	?	?	+	−	+	+
Burci et al. (2013)	+	+	?	+	?	?	+	?	+	+
Megala and Geetha (2012)	+	+	?	+	?	?	+	?	+	+
Sharma et al. (2012)	+	+	−	+	?	?	+	?	+	+
Bansal and Goel (2012)	+	+	−	+	?	?	+	?	+	+
Kim et al. (2012)	+	+	−	+	?	?	+	?	+	?
Das and Roy (2012)	+	+	−	+	?	?	+	−	+	+
Vijayakumar et al. (2011)	+	+	?	+	?	?	+	−	+	+
Abdallah et al. (2011)	+	+	?	+	?	?	+	?	+	?
Rozza et al. (2011)	+	+	?	+	?	?	+	?	+	+
Lakshmi et al. (2010)	+	+	−	?	?	?	+	?	+	+
da Silva Quirino et al. (2009)	+	+	?	+	?	?	+	?	+	+
Rachchh and Jain (2008)	+	+	−	?	?	?	+	?	+	?
Rao et al. (2008)	+	+	?	+	?	?	+	−	+	+
Jainu and Devi (2006)	+	+	?	+	?	?	+	−	+	+
Valcheva-Kuzmanova et al. (2005)	+	+	?	+	?	?	+	−	+	+

(Continues)

TABLE 3 | (Continued)

References	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
Al-Qarawi et al. (2005)	+	+	?	+	?	?	+	−	+	+
Ajaikumar et al. (2005)	+	+	−	?	?	?	+	−	+	?
Mahendran et al. (2002)	+	+	?	+	?	?	+	−	+	?
Mesia-Vela et al. (2002)	+	+	−	?	?	?	+	−	+	?
Jafri et al. (2001)	+	+	?	+	?	?	+	−	+	+
Rao et al. (2001)	+	+	?	+	?	?	+	−	+	+

Note: Each included study was analyzed by the authors following the judgment questions (P1–P10) and classified according to its risk of bias. Orange (?): Unclear/uncertain risk of bias; red (−): High risk of bias; blue (+): Low risk of bias. The questions and judgments are in the Supporting Information section.

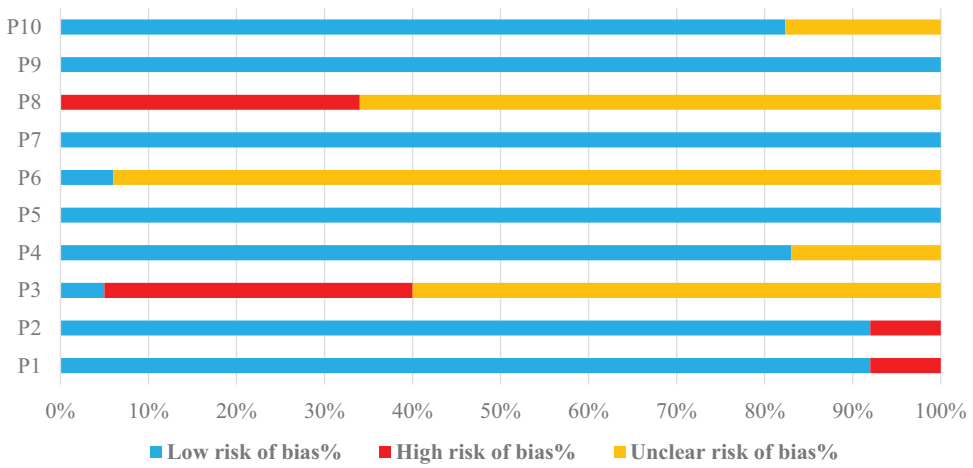


FIGURE 4 | The risk of bias scale indicates the proportion of articles that met each criterion.

signaling pathway, these compounds reduce the production of TNF-α, IL-1β, and IL-6, thereby alleviating gastric inflammation (Kany et al. 2019).

Fruits such as *A. chinensis, S. chinensis, P. sinensis, C. sinensis, Opuntia ficus, and C. myxa* have demonstrated significant potential in experimental studies to reduce gastric inflammation, based on their ability to regulate the production of pro-inflammatory cytokines.

3.3.3 | Stimulators of Prostaglandin Synthesis

Prostaglandins, especially prostaglandin E2 (PGE_2), play a crucial role in maintaining the integrity of the gastric mucosa (Lopes et al. 2020). They are synthesized from arachidonic acid through the action of the enzymes COX-1 and COX-2. (Miller 1983). In the stomach, prostaglandins protect the gastric mucosa by increasing the secretion of mucus and bicarbonate, decreasing gastric acid secretion, and improving blood flow in the mucosa (Gudis and Sakamoto 2005). These synergistic actions create a protective barrier against harmful agents, such as hydrochloric acid and pepsin (Heeney et al. 2021).

Inhibition of prostaglandin production, for example, by NSAIDs, results in a reduction of the protective barrier of the gastric mucosa, which can lead to the development of gastric ulcers (Pineda-Peña and Chávez-Piña 2023). In this context, studies on fruits with gastroprotective properties have shown that they stimulate the production of prostaglandins, helping to restore the protective barrier and prevent damage to the mucosa.

The studies included in this review indicate that species, such as *A. chinensis*, *P. dulce*, *C. myxa*, and *C. lemon* (CL), activate the COX-2 pathway, promoting the synthesis of PGE_2 and protecting the gastric mucosa. Thus, the increased synthesis of prostaglandins emerges as one of the primary mechanisms by which fruits with gastroprotective properties exert their beneficial effects.

3.3.4 | Inhibitors of H^+/K^+ ATPase

The H^+/K^+ ATPase, also known as the proton pump, is a crucial enzyme located in the parietal cells of the stomach, responsible for the secretion of gastric acid (Adinortey and N'guessan 2022). This process involves the transport of hydrogen ions (H^+) into the stomach lumen in exchange for potassium ions (K^+), acidifying the gastric environment, which is necessary for food digestion and the activation of the enzyme pepsin (Idrees and Saeed 2021). However, excessive production of gastric acid can lead to

conditions such as gastritis, gastric ulcers, and gastroesophageal reflux. Therefore, the inhibition of H^+/K^+ ATPase is a relevant therapeutic target in the treatment of these diseases (Beil et al. 1994).

Fruits with gastroprotective properties can natural inhibitors of the proton pump, reducing gastric acidity and protecting the mucosa from the corrosive action of acid. Many compounds found in fruits have demonstrated the ability to inhibit H^+/K^+ ATPase in a manner similar to synthetic PPIs, such as omeprazole (Lorentzon et al. 1985). The difference lies in the less aggressive nature of these natural compounds, which do not present side effects (Adinortey and N'guessan 2022).

Additionally, studies with extracts from fruits such as *M. nigra*, *R. niveus*, *P. dulce*, *M. dioica*, *F. glomerata*, and *S. nigrum* have shown a reduction in gastric acid secretion due to the inhibition of H^+/K^+ ATPase. The mechanism of action of these fruits includes competitive inhibition of potassium ion binding at the active site of the enzyme, reducing acid secretion without compromising the acid-base balance of the stomach. This inhibition protects the gastric mucosa from damage and promotes the healing of existing lesions.

3.3.5 | Modulation of Pepsin, Gastrin, and Mucin

Pepsin is a crucial proteolytic enzyme for protein digestion in the stomach. It is secreted in an inactive form called pepsinogen by the chief cells of the gastric mucosa and is activated by the acidity of gastric juice, transforming into pepsin (Fornai et al. 2011; Yandrapu and Sarosiek 2015). This enzyme plays a crucial role in breaking down food proteins into smaller peptides, facilitating digestion. However, excess pepsin, associated with a highly acidic environment, can contribute to the formation of gastric ulcers and damage to the mucosa (Patil et al. 2015; Silva and Florenco de Sousa 2011). Various medicinal plants have been studied for their ability to modulate pepsin activity and protect the gastric mucosa. In this study, the species that exhibited this effect were *E. officinalis*, *A. subulatum*, *P. dulce*, *C. oblonga*, and *T. dioica*.

Gastrin, in turn, is a hormone secreted by G cells in the gastric antrum in response to the presence of food in the stomach (Dong and Xin 2022). It stimulates the secretion of hydrochloric acid by parietal cells and also increases the production of pepsinogen. This mechanism is part of the homeostatic control of digestion; however, elevated levels of gastrin can lead to gastric hyperacidity, promoting the development of peptic ulcers and gastritis (Rehfeld 2021). Plant extracts from species such as *P. dactylifera*, *S. nigrum*, *P. tuberculatum*, and *P. dactylifera* act directly on G cells, inhibiting the secretion of gastrin or modulating the signaling pathways that activate acid secretion.

Regarding mucin, it is an essential glycoprotein for the protection of the gastric mucosa, as it forms a mucus layer that acts as a physical barrier against aggressive agents, such as gastric acid and digestive enzymes (Vandeerveen et al. 2021). Fruits with gastroprotective activity have been shown to be effective in stimulating the production and secretion of mucin, reinforcing this protective barrier (Mota da Silva et al. 2020).

Species such as *E. officinalis*, *P. dactylifera*, *X. granatum*, *C. myxa*, *A. nilotica*, *P. dulce*, *M. nigra*, *R. niveus*, and *C. reitziana* have been reported in experimental studies for promoting increased mucin secretion, contributing to the integrity of the gastric mucosa, and helping to prevent lesions induced by oxidative stress and inflammation. This mechanism is essential for maintaining gastric homeostasis and protecting against ulcers and gastritis (Cipou et al. 2022).

Additionally, these species can also stimulate mucin production by gastric mucosal cells, strengthening the protective barrier against gastric acid and digestive enzymes. This synergistic action between the reduction of pepsin activity, increased mucin secretion, and modulation of gastrin levels is essential for preventing conditions related to hyperacidity and gastric lesions (Corfield et al. 2000; Niv 2015). Thus, the consumption of fruits that inhibit these mechanisms can contribute to the treatment of gastrointestinal disorders and improve gastric health.

3.4 | Bioactive Compounds and Integrated Mechanisms of Gastroprotection

The gastroprotective potential of fruits is strongly linked to their diverse composition of bioactive compounds, particularly polyphenols, flavonoids (such as quercetin, rutin, kaempferol, and naringenin), phenolic acids (e.g., gallic acid and ferulic acid), carotenoids (e.g., β-carotene, and lycopene), vitamins C and E, and polysaccharides. These compounds act at various cellular levels, influencing antioxidant defense, inflammatory modulation, and gastric mucosal integrity (Chiu et al. 2021; Garrido-Valdes et al. 2023).

Flavonoids and polyphenols, abundantly present in *P. dactylifera*, *V. corymbosum*, *C. sinensis*, and *P. granatum*, for instance, have been shown to upregulate the Nrf2/ARE pathway, which leads to increased expression of antioxidant enzymes such as SOD, CAT, and GPx (Abdelghffar et al. 2022; Thiruvengadam et al. 2021). Simultaneously, they inhibit the activation of NF-κB, a transcription factor that regulates the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, thereby contributing to the reduction of oxidative stress and inflammation in the gastric mucosa (Moneva-Sakelarieva et al. 2025).

The interaction of bioactive compounds with signaling pathways also affects epithelial protection. Some fruits, such as *S. chinensis*, *C. myxa*, and CL, stimulate prostaglandin synthesis via COX-2, promoting mucus and bicarbonate secretion and improving mucosal blood flow (Abdallah et al. 2011; Selmi et al. 2017; Si et al. 2020). Others, including *M. nigra*, *R. niveus*, and *F. glomerata*, demonstrate inhibitory effects on H^+/K^+-ATPase (proton pump), reducing gastric acid secretion without disrupting acid-base homeostasis (Krishnaiah et al. 2011; Nesello et al. 2017). This inhibition is often accompanied by modulation of potassium channels, leading to membrane hyperpolarization, reduced intracellular calcium influx, and activation of protein kinase C (PKC), which together reinforce the cytoprotective effects on gastric epithelial cells (Cosme et al. 2021).

Additionally, some bioactive compounds promote increased mucin secretion and inhibit pepsin activity, contributing to the formation of a stable mucosal barrier. This barrier protects epithelial cells from the damaging effects of hydrochloric acid and digestive enzymes. Fruits like *E. officinalis*, *X. granatum*, and *P. dulce* have shown effects on all these fronts, enhancing mucin production and restoring mucosal architecture (Genwali et al. 2013; Lakshmi et al. 2010; Megala and Geetha 2015).

Importantly, these mechanisms do not act in isolation. For instance, enhanced antioxidant capacity not only reduces ROS-mediated mucosal injury but also indirectly downregulates inflammatory cascades by inhibiting NF-κB and upregulating cytoprotective prostaglandins (Moneva-Sakelarieva et al. 2025). Likewise, potassium channel activation influences calcium signaling and PKC pathways, contributing to tissue repair and modulation of mucus secretion (Miranda et al. 2023). This integrative effect underscores the multifactorial nature of the gastroprotection induced by fruits.

Among the species evaluated, some stood out due to their ability to simultaneously modulate multiple protective mechanisms, rich bioactive content, and consistency of effects across studies. The species *H. polyrhizus*, *P. dactylifera*, *V. corymbosum*, *A. marmelos*, *P. edulis*, *P. granatum*, *C. sinensis*, *C. oblonga*, *S. chinensis*, and *A. melanocarpa* were identified as the most relevant species. These fruits demonstrated potent antioxidant activity (via the Nrf2 pathway), anti-inflammatory effects (through NF-κB inhibition and cytokine modulation), stimulation of prostaglandin and mucin secretion, and inhibition of gastric acid secretion via proton pump blockade. The recurrence of these findings in various experimental models reinforces their therapeutic potential and highlights their value for the development of dietary and phytotherapeutic interventions aimed at protecting the gastric mucosa.

4 | Conclusion

This systematic review highlighted the promising role of fruits as sources of bioactive compounds with potential to prevent and treat gastrointestinal diseases. The studies analyzed showed that the mechanisms of action involved in the gastroprotective response of various fruit species include modulation of antioxidant defenses, regulation of inflammatory and molecular mediators such as prostaglandins, nitric oxide, potassium channels, pepsin, gastrin, α_2 adrenergic receptors, histamine receptors, and muscarinic receptors, as well as myeloperoxidase and mucin. Although the results are encouraging, the studies were conducted in preclinical models, pointing to the need for more robust clinical trials to assess the efficacy and safety of these species in humans. Furthermore, the complexity of the observed mechanisms of action suggests that these species may be used not only in isolation but also in combined formulations to enhance therapeutic efficacy. Considering the increasing interest in natural products with fewer side effects, these findings support the potential development of complementary therapies, emphasizing the importance of future in vivo and clinical studies to validate and integrate these bioactive compounds into current treatment strategies.

Author Contributions

All authors contributed substantially to the conception, development, writing, and revision of the manuscript and approved the final version for publication.

Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supplementary Material: fft270117-sup-0001-SuppMat.xlsx